

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

APPLICANT : SAMUEL ROSE, MD  
SERIAL NO. : 08/782,590  
FILED : January 13, 1997  
FOR : A METHOD AND COMPOSITION FOR  
TREATING CANCER BY CONVERTING  
SOLUBLE RADIOACTIVE TOXIC  
AGENTS INTO INSOLUBLE  
RADIOACTIVE TOXIC PRECIPITATES  
VIA THE ACTION OF NON-  
MAMMALIAN ENZYMES BOUND TO  
THE NON-ENDOCYTOSING  
RECEPTORS OF TARGET CELLS  
EXAMINER : Susan Unger Ph.D.  
Group Art Unit : 1640

Commissioner of Patents and Trademarks  
Washington, D.C. 20231

**DECLARATION UNDER 35 U.S.C. 1.132 TRAVERSING GROUNDS OF REJECTION**

SIR:

1. I, Emeritus Professor of Chemistry at the University of California at Berkeley, Henry Rapoport, Ph.D., hereby declare that I am a citizen of the United States and a resident of Berkeley, California.

### **BACKGROUND**

2. I am currently Emeritus Professor of Chemistry at the University of California, Berkeley. I have been teaching Chemistry at U.C. Berkeley since 1946 and have been a Professor since 1957 and was former Chairman of the Chemistry Department. During my tenure I have received numerous fellowships, lectureships, and awards. I have also served on the editorial boards of numerous journals including the Journal of Medicinal Chemistry and the Journal of Organic Chemistry where I am currently a Senior Editor. In my career I have published over 440 articles spanning a broad range of topics in the field of organic and synthetic chemistry.

3. I make this declaration under 37 C.F.R. 1.132 to traverse grounds of rejection of the above-identified U.S. Patent Application, Serial No. 08/782,590 of Samuel Rose, MD (hereinafter the '590 Application).

4. I have examined and am familiar with the original specification, claims, and drawings of the '590 Application; the Official Action mailed March 18, 1998; the Amendment filed September 21, 1998; and the Official Action mailed November 25, 1998.

### **REGARDING OFFICIAL ACTION MAILED NOVEMBER 25, 1998, PAPER NUMBER 18 (HEREINAFTER "ACTION")**

#### **5. Regarding Action, Section 5(a'), page 4**

Sufficient detail of the invention is described in the specification of the patent application (pages 20-24) for an individual who has experience in organic and synthetic chemistry to make the various soluble precipitable materials described in this patent application.

The indoxyl class of soluble precipitable materials disclosed in the patent application can be readily made by manipulating well-known aspects of the various indoxyl compounds. The synthesis work is technically complex, but given the information disclosed in the specification of the application and in view of the understanding of those skilled in the field, these reagents can readily be made. The dimerizing function of indoxyl compounds via enzyme action where the molecule forms a reactive intermediate which is rapidly oxidized and self-condenses to form a new molecule (for example indigo) is well-known in the field, has been widely published, and has been disclosed in the specification of the application. The specification of the application also discloses a number of variations of indoxyl compounds which can be readily made by one skilled in the art by adding functional and/or reactive groups, dependent chains, or spacer molecules to the different positions of the basic indoxyl, to alter the dimerization process or the final product of the reaction. For example, on page 21 and in Figs. 11-12 of the application, Dr. Rose discloses how the attachment of a lactam can be made via the phosphate group to the indoxyl at position 3. Thus, given the information disclosed in the application, one skilled in the art could readily make this indoxyl variant.

The disclosure of the present invention (page 23-24) also enables one skilled in the art to make soluble precipitable materials by attaching a solubilizing polymer to an insoluble chemical. It is well-known in the field and to one skilled in the art that the attachment of certain solubilizing molecules to any number of insoluble chemicals or agents results in the final product being soluble and that if the bond between the two moieties is later cleaved, the insoluble compound will precipitate. Given the disclosure and the example used in the specification of the application, one skilled in the art could make the soluble precipitable materials disclosed by Dr. Rose. The synthesis required for these types of soluble precipitable materials (compared to the indoxyl class) is less difficult.

The disclosure in the specification of Dr. Rose's patent application enables one skilled in the art to radio-label the soluble precipitable material. Radio-labeling of the indoxyl class of soluble precipitable materials is described on page 23, Figs. 15-17 of the application. Regarding the second class of soluble precipitable materials, the process of radio-labeling virtually any insoluble chemical is well-known to one skilled in the art, has been published, and can be easily achieved.

Regarding Action, Section 8, pages 6, 7

Sufficient details are disclosed in the specification of the patent application (page 19) for one who is skilled in the art and who has experience in organic chemistry to attach molecules to the soluble precipitable materials to make them cell impermeant. In particular, one skilled in the art can attach the molecules to the first therapeutic agent. The molecules which would make the soluble precipitable material into a cell impermeable molecule can be anionic molecules and/or large molecules, such as polymers or peptides, greater than 1000 Daltons. It is well-known to one who is skilled in the art (and frequently practiced) that attachment of such molecules makes cell permeant chemicals, cell impermeant.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date:

May 24, 1999

Signed:

Henry Rapoport